Total Synthesis of Millingtonine

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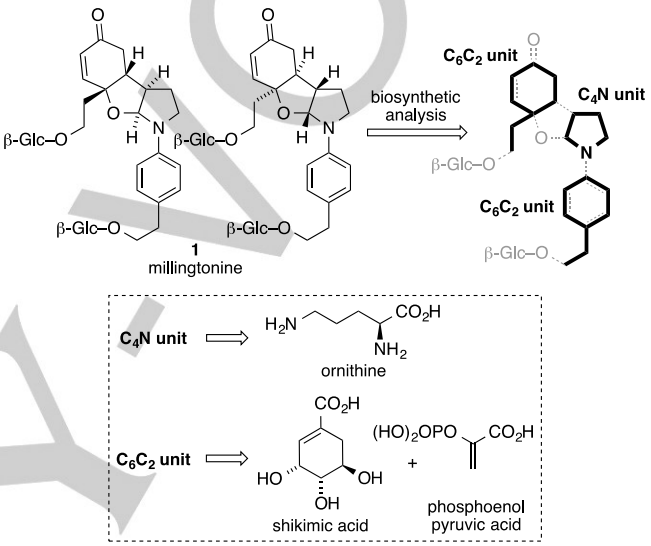
Patrick D. Brown, and Andrew L. Lawrence*

Abstract: Millingtonine is a glycosidic alkaloid that exists as a pair of pseudo-enantiomeric diastereomers. Consideration of the likely biosynthetic origins of this unusual natural product has resulted in the development of a seven-step total synthesis. Results from this synthetic work provide evidence in support of a proposed network of biosynthetic pathways that can account for the formation of several phenylethanoid natural products.

In 1996 Yamasaki and co-workers isolated the alkaloid millingtonine (**1**) from *Millingtonia hortensis*, an ornamental Bignonia plant more commonly known as the Indian Cork Tree.[1] Millingtonine (**1**) was isolated as a mixture of two diastereomeric alkaloids, which contain a molecular framework not previously known to exist in the natural world. Conceptually, but not biosynthetically (*vide infra*), millingtonine (**1**) can be considered to consist of a racemic aglycone core that is 'resolved' into two pseudo-enantiomeric diastereomers by the attachment of a pair of β-D-glucopyranosyl units. Biosynthetically, millingtonine (**1**) is likely constructed from two shikimate-derived C_6C_2 units, linked together by an ornithine-derived C_4N unit (Scheme 1). No biosynthetic pathway towards millingtonine (**1**) has been proposed and, as commented upon by the isolation team, *"the mechanism of insertion of this (C_4N) unit between the two C_6C_2 units is unknown"*.[1]

There has been one previous total synthesis of millingtonine (**1**), reported in 2012 by the research groups of Ley, Kirschning and Baxendale.[2] The execution of a total synthesis of this alkaloid is an impressive achievement, with the intermediate structures en-route to millingtonine (**1**) reported to be *"exceedingly prone"* to rearrangement reactions. In total, the Ley-Kirschning-Baxendale synthesis required twelve linear steps from commercially available materials (sixteen steps in total) and produced milligram quantities of material. We were hopeful that if we could gain new insight into how nature synthesizes millingtonine (**1**) we might be able to develop a new, more step-economical, synthetic strategy.

Our previous biomimetic studies on other phenylethanoid natural products provided some important clues as to the potential origins of millingtonine (**1**).[3] We considered that a phenylethanoid glycoside **2**, which contains an ornithine-derived *N*-linked putrescine unit, might represent a reasonable biosynthetic precursor. Our biosynthetic proposal, which is shown in Scheme 2, involves a network of pathways that can account for the formation of several structurally distinct natural products isolated from Bignoniaceae plants: cornoside (**3**),[4] rengyolone (**4**),[5] incarviditone (**5**),[6] incarvilleatone (**6**),[7] incargranine B (**7**),[8] and millingtonine (**1**).[1]



Scheme 1. Structure and retro-biosynthetic analysis of millingtonine (**1**). Glc = D-glucopyranosyl.

In our proposal, diamine **2** can undergo an oxidative dearomatization to form imine **8** (Scheme 2; Pathway 1), which following hydrolysis would give the known *para*-quinol natural product cornoside (**3**). It has been shown that cleavage of the glycosidic bond in cornoside (**3**) results in concomitant *oxa*-Michael cyclisation to give the racemic natural product rengyolone (**4**).[9] We previously investigated a biomimetic domino-Michael dimerization of rengyolone (**4**) to access incarviditone (**5**),[3a] a racemic homochiral dimer. From our synthetic studies we were able to reassign the relative stereochemistry of incarviditone (**5**) and isolate an unexpected racemic heterochiral dimer, which was subsequently reported as a natural product named incarvilleatone (**6**).[7] An alternative biosynthetic pathway from diamine **2** (Scheme 2; Pathway 2) involves oxidative deamination to give amino-aldehyde **9**, which would be expected to undergo intramolecular condensation to give enamine **10**. We predicted enamine **10** would then undergo rapid dimerization with its corresponding iminium ion **11**, which formed the basis of our previous structural reassignment and biomimetic synthesis of incargarnine B (**7**).[3b]

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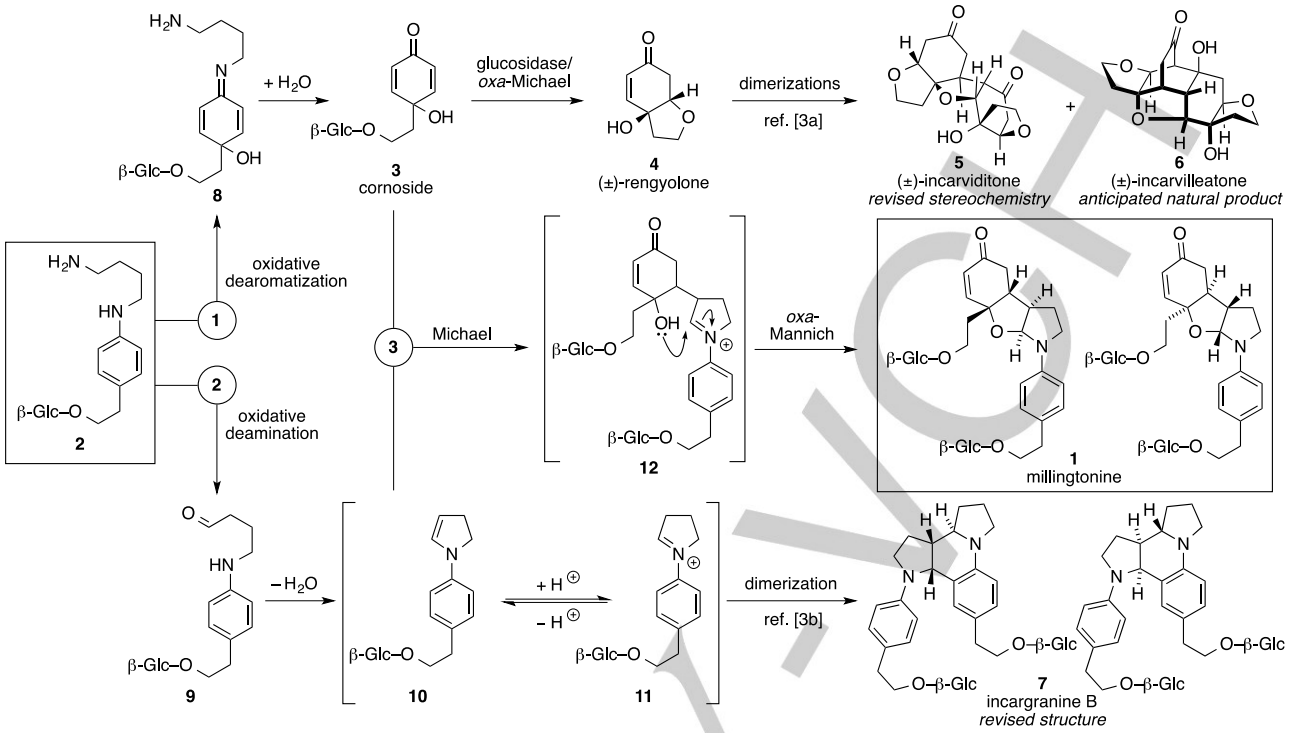
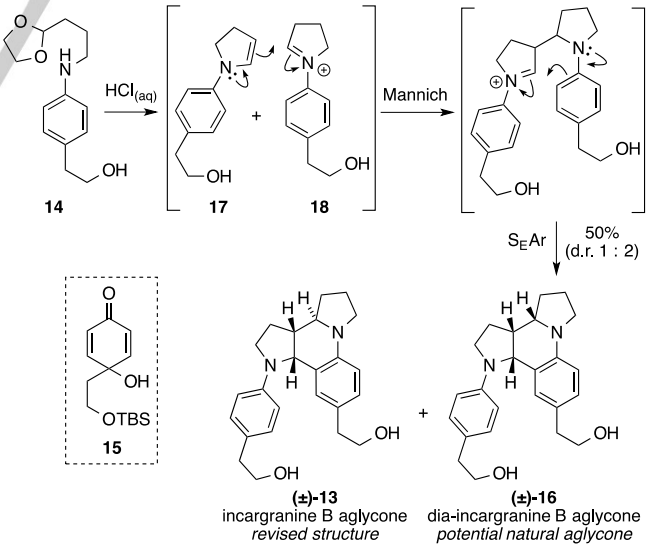


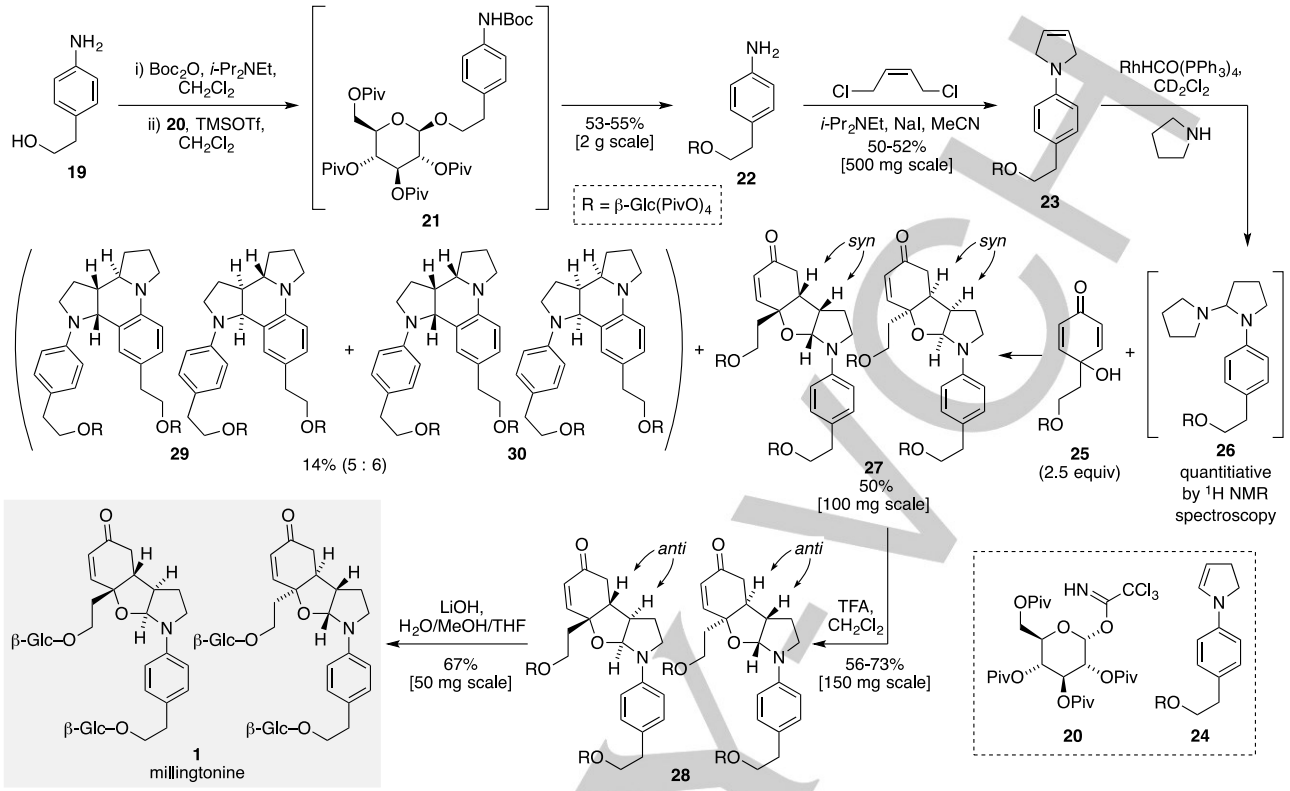
Scheme 2. Proposed network of biosynthetic pathways towards a family of plant-derived phenylethanoid natural products, including millingtonine (**1**). Glc = D-glucopyranosyl.

With these two divergent biosynthetic pathways in mind we recognized the possibility that the two pathways could re-converge to give millingtonine (**1**) (Scheme 2; Pathway 3). Thus, a Michael reaction between enamine **10** and cornoside (**3**) would give an intermediate iminium ion **12**, which would rapidly ring-close through an *oxa*-Mannich reaction to give millingtonine (**1**). Therefore, in our proposed biogenesis, the two diastereomers of millingtonine (**1**) are the result of a lack of stereochemical influence exerted by the sugars of enamine **10** and cornoside (**3**) in a crossed-dimerization, rather than a late-stage glucosidation of a racemic aglycone.

In our previous work (Scheme 3),[3b] the incargranine B framework (**13**) was accessed through a biomimetic domino Mannich/S_EAr (electrophilic aromatic substitution) reaction sequence, initiated by acidic-deprotection of acetal-protected amino-aldehyde **14**.[10] It was envisaged that having *para*-quinol **15**[11] present under these acidic deprotection conditions would allow for a biomimetic crossed-dimerization to occur to give the millingtonine framework. However, after extensive experimentation, screening various acidic reaction conditions, no crossed-dimerizations could be achieved. Only formation of the incargranine B and dia-incargranine B aglycone structures (**13** & **16**) was observed. It was concluded that the domino Mannich/S_EAr reaction sequences, en-route to the incargranine B frameworks, are too fast for crossed-dimerization to compete. We considered, however, that a window of opportunity for crossed-dimerization might exist if an *N*-aryl enamine (akin to **17**) could be accessed whilst avoiding formation of the highly electrophilic *N*-aryl iminium species (akin to **18**).

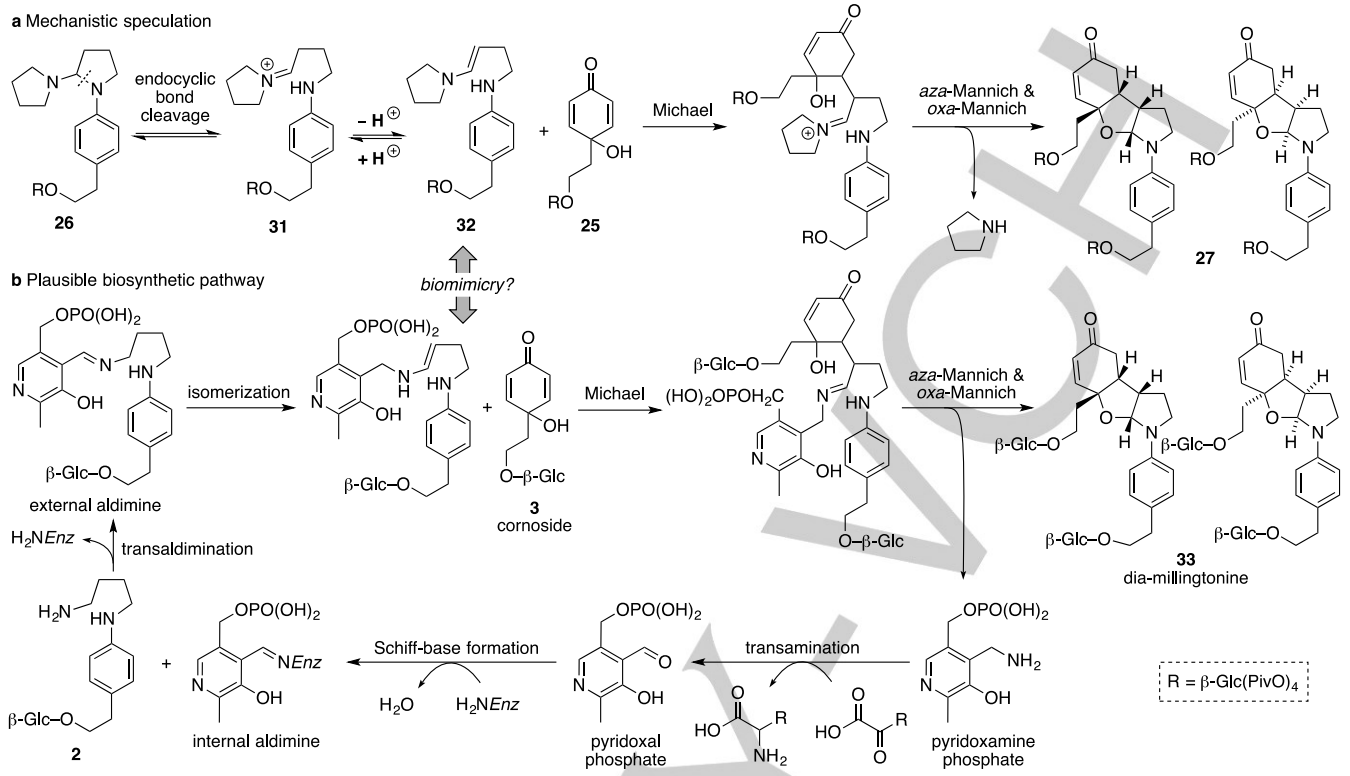


Scheme 3. Previously reported biomimetic synthesis of the incargranine B aglycone **13**.[3b] TBS = *tert*-butyldimethylsilyl.



Scheme 4. Biomimetic total synthesis of millingtonine (**1**). Boc = *tert*-butyloxycarbonyl, TMSOTf = trimethylsilyl trifluoromethanesulfonate, Glc = D-glucopyranosyl, Piv = pivaloyl, TFA = trifluoroacetic acid.

Many strategies were investigated before we settled upon an alkene isomerization approach, using transition-metal hydride catalysis.[12] Thus, commercially available 4-aminophenethyl alcohol **19** was protected as an acid-labile *tert*-butoxycarbamate before a β-selective glucosidation was achieved, using the pivaloyl-protected trichloroacetimidate **20** (Scheme 4).[13] Under the acidic glucosidation reaction conditions deprotection of aniline **21** occurred *in situ* to give the pivaloyl-protected glucoside **22** in 53-55% yield over the two steps. Condensation of aniline **22** with (*Z*)-1,4-dichlorobut-2-ene then gave *N*-aryl-2,5-dihydropyrrole **23** in 50-52% yield.[14] It was found that the commercially available $RhHCO(PPh_3)_4$ was a competent catalyst for the isomerization of skipped enamine **23** into the conjugated enamine **24**.[15] All efforts to purify and isolate enamine **24**, however, were met with failure. Therefore, the search for suitable reaction conditions for cross-dimerization of enamine **24** with *para*-quinol **25**, which was prepared in 4 steps from tyrosol,[16] were pursued using freshly prepared solutions of enamine **24**. Pyrrolidine was investigated, in the hope of establishing an iminium-organocatalytic cycle,[17] and gratifyingly led to crossed-dimerization for the first time, albeit in very low yield. Control experiments, however, revealed that the beneficial effect of adding pyrrolidine was down to the unexpected formation of an aminal intermediate **26**.[15] Furthermore, inclusion of pyrrolidine at the beginning of the rhodium-hydride-catalyzed isomerization reaction was found to result in quantitative conversion of alkene **23** to aminal **26**.[18] Pivaloyl-protected cornoside **25** was then added to this freshly prepared solution resulting in the formation of a 1:1 diastereomeric mixture of crossed-dimers **27** in 50% isolated yield. Formation of the *cis*,*syn*,*cis*-isomers **27** was an unexpected and presumably kinetically controlled outcome, as we anticipated the desired *cis*,*anti*,*cis* ring system would be thermodynamically more favorable. Our kinetic versus thermodynamic reasoning was shown to be sound, as exposure of the *cis*,*syn*,*cis*-isomers **27** to acidic conditions resulted in isomerization to the desired *cis*,*anti*,*cis*-isomers **28** in 56-73% yield (Scheme 4). Presumably this isomerization occurs via an acid-catalyzed retro-*oxa*-Mannich/iminium-epimerization/*oxa*-Mannich reaction sequence. Finally, removal of the pivaloyl groups under basic conditions gave over 50 mg of millingtonine (**1**) in 67% yield. Thus we had successfully synthesized millingtonine (**1**) in a longest linear sequence of seven steps from commercially available materials (ten steps in total), which compares favorably to the previous state-of-the-art.[2]



Scheme 5. a, Mechanistic speculation for our successful crossed-dimerization. **b**, Plausible biosynthetic pathway towards dia-millingtonine (**33**) involving vitamin B6 (*i.e.*, pyridoxal phosphate) as a co-enzyme. Glc = D-glucopyranosyl.

The successful crossed-dimerization of aminal **26** with *para*-quinol **25** (Scheme 4) stands in stark contrast to the exclusive homo-dimerization observed when using acetal **14** (Scheme 3). Our failure to cross-dimerize acetal **14** was attributed to the formation of a highly reactive *N*-aryl iminium species **18**, which leads to very fast and essentially irreversible domino Mannich/S_EAr reaction sequences (Scheme 3). In our successful crossed-dimerization, however, we still isolate an 14% yield of homo-dimers (**29** and **30**) (Scheme 4), indicating that an *N*-aryl iminium ion must still be formed under these reaction conditions. *How then can crossed-dimerization compete?* One possible explanation is that it is more favourable for the endocyclic C–N bond of aminal **26** to cleave, in preference to the exocyclic C–N bond, to give the acyclic iminium ion **31** (Scheme 5a). Therefore, the problematic *N*-aryl iminium species is present at lower concentration and can also be rapidly trapped by the pyrrolidine. Thus enamine **32**, which would also be expected to be more nucleophilic than the *N*-aryl enamine **24**, has a sufficient window of opportunity to react with *para*-quinol **25** (Scheme 5a). It is interesting to consider whether this might, therefore, be indicative of a similar mechanism operating within the plant. Might pyrrolidine be mimicking the coenzyme-role of vitamin B6 (*i.e.*, pyridoxal phosphate) in an interrupted oxidative-deamination reaction of diamine **2** (Scheme 5b)?[19]

In summary, through synthesis alone we have been able to probe the feasibility of our proposed biogenesis of millingtonine (**1**). We have been able to obtain evidence in support of a unified network of biosynthetic pathways that can account for the formation of a family of phenylethanoid natural products. Crucially, these new biosynthetic insights have enabled the development of a highly step-economical total synthesis of millingtonine (**1**). Central to the development of this successful synthesis was the use of transition-metal hydride catalysis to access an otherwise unstable biomimetic intermediate, an approach we envisage will prove applicable to other biomimetic studies. The future isolation of the *cis*,*syn*,*cis*-isomer of millingtonine, namely dia-millingtonine (**33**), from the natural environment would represent a new case of 'natural product anticipation' – an essentially unique benefit of following biomimetic strategies in synthesis.[20]

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Keywords: alkaloids • biomimetic synthesis • domino reactions • natural products • phenylethanoids

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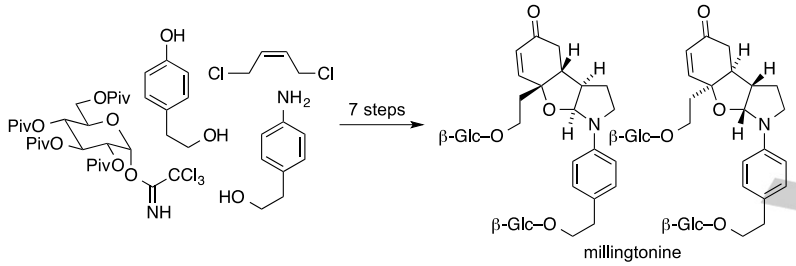

Hidden symmetry: Millingtonine is a glycosidic alkaloid that exists as a pair of pseudo-enantiomeric diastereomers. Consideration of the likely biosynthetic origins of this unusual natural product has resulted in the development of a seven-step total synthesis. Results from this synthetic work provide evidence in support of a proposed network of biosynthetic pathways that can account for the formation of several phenylethanoid natural products.